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APPLICATION

for

UNITED STATES LETTERS PATENT

POLYMERIZABLE COMPOSITIONS AND METHODS OF USE

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POLYMERIZABLE COMPOSITIONS AND METHODS OF USE

[0001] This application is a continuation-in-part of U.S. Application Serial No. 09/577,115, filed May 23, 2000, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to organic compositions and more specifically to polymerizable compositions and methods of use therefor.

BACKGROUND OF THE INVENTION

[0003] Research in organic polymer chemistry has led to the discovery of a variety of biocompatible polymeric materials. One important class of such materials is the cyanoacrylates. These materials have been used successfully in a variety of medical applications where traditional medical techniques or devices have been found wanting, such as for example, tissue adhesives, endovascular embolic agents, and the like. tissue adhesives have been in clinical endovascular use since the 1970's. Liquid acrylics are extremely useful as endovascular embolic agents because of their ability to create permanent vascular occlusion. Typical complications associated with the use of cyanoacrylates for embolization occur when there is occlusion of normal arterial branches or material penetration into critical venous outflow channels. Additionally, reflux of cyanoacrylate materials around the delivery catheter tip can result in permanent endovascular - catheter adhesion and attempts at withdrawal the catheter can produce catheter fracture, vascular damage with resultant dissection/occlusion, or avulsion of the involved vascular pedicle with resultant subarachnoid hemorrhage.

[0004] Alkyl α-cyanoacrylates are a homologous series of organic molecules which readily polymerize and can adhere to living tissues. The methyl homolog has been used in hemeostasis and non-suture wound closure since 1960.

[0005] Polymerization rate of alkyl α-cyanoacrylates is a function of alkyl chain length. It has been reported that alkyl α-cyanoacrylates with six or fewer carbon atoms in the alkyl chain polymerize rapidly upon contact with animal tissue.

[0006] Since the advent of *n*-butyl-2- cyanoacrylate, there has been little advancement in the science of cyanoacrylate embolization of vascular structures such as arteriovenous malformations (AVM). Several properties of cyanoacrylates are advantageous for such embolizations, e.g. tissue adhesion, rapid polymerization when contacted with blood and tissue, and long-term biocompatibility. Rapid polymerization allows the liquid material to solidify in flowing blood inside arteries without passing through small channels into venous structures. However, this rapid endothermic polymerization may also release sufficient heat to damage surrounding tissue, for example, brain tissue.

[0007] Although catheter coatings have been developed to reduce the risk of inadvertent endovascular catheter fixation during embolization procedures. catheter - cyanoacrylate adhesion remains a problem during intravascular embolization. Also, the level of practitioner proficiency and the specific adhesive composition utilized play a major roles in these events.

[0008] Accordingly, there exists a continuing need for compositions that have the correct balance of polymerization rate, adhesiveness, biocompatibility, and radiopacity. The present invention describes such compositions.

SUMMARY OF THE INVENTION

[0009] In accordance with the present invention, there are provided compositions including a first component and a second component, wherein the first component includes at least two polymerizable organic monomers and wherein the second component includes an organic oligomer, a plasticizer, and an opacificant agent, wherein the total composition polymerizes upon contact with an anionic environment. The compositions of the present invention are useful for filling or partially filling and occluding, or partially occluding cavities or spaces in human or animal bodies. The invention compositions are also useful for ablating diseased or undesired tissue or organs by blocking the blood supply to the tissue or organs.

[0010] In another aspect of the present invention, there are provided methods for filling or partially filling and occluding or partially occluding cavities or spaces in a human or animal bodies. Another aspect of the present invention provides methods for ablating diseased or undesired tissue or organs by blocking the blood supply to the tissue or organs. Other aspects of the present invention provide methods for treating arteriovenous malformations (AVM), methods for treating neural aneurysms, methods for treating uterine fibroids, methods for treating solid tumors, methods for treating uterine leiomyoma, and methods for sterilizing female mammals.

[0011] In a still further aspect of the invention, there are provided methods for the controlled delivery and fixation of therapeutic compositions, chemotherapeutic compositions, radiation devices, magnetic particles, or other agents to desired location in human or animal bodies.

[0012] In yet another aspect of the invention, there are provided methods for adhering a first section of mammalian tissue to either a second section of mammalian tissue or a non-tissue surface.

DETAILED DESCRIPTION OF THE INVENTION

[0013] The present invention provides compositions including a first component and a second component, wherein the first component includes at least two polymerizable organic monomers and wherein the second component includes an organic oligomer, a plasticizer, and an opacificant agent, wherein the total composition polymerizes upon contact with an anionic environment.

[0014] The composition is useful for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space"). In particular, the composition is useful for filling an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition; the composition is also useful for adhering tissue to tissue, or adhering tissue to a device. The composition has the property of polymerizing when it comes in contact with an anionic environment, or when it is deployed *in situ* in an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition.

[0015] In a preferred embodiment, the composition includes alkyl cyanoacrylates. In a particularly preferred embodiment, the first component of the composition includes, *n*-hexyl cyanoacrylate and methyl cyanoacrylate or 2-hexyl cyanoacrylate and methyl cyanoacrylate.

[0016] In another preferred embodiment, the second component includes an oligomer or polymer formed from a composition of alkyl cyanoacrylate monomer, an alkyl esterified fatty acid and an opacificant agent.

[0017] In yet another embodiment, the second component of the composition includes a halogenated oil. Preferred are iodinated and brominated oils.

[0018] In a still further preferred embodiment, the first component is comprised of two alkyl cyanoacrylate monomers, and at least one inhibitor. A particularly preferred embodiment of the first component includes n-hexyl cyanoacrylate, methyl cyanoacrylate and one inhibitor.

[0019] A particularly preferred composition includes a first component and a second component, wherein the first component includes methyl cyanoacrylate, *n*-hexyl cyanoacrylate, hydroquinone, *p*-methoxyphenol, and acetic acid, and wherein the second component includes an oligomer or polymer formed from *n*-hexyl cyanoacrylate monomer, an alkyl esterified fatty acid and an opacificant agent. In a most preferred embodiment, the alkyl esterified fatty acid is ethyl myristate and the opacificant agent is gold.

[0020] It is known to those of ordinary skill in the art that the predictability of polymerization properties of alkyl cyanoacrylate monomers is related to the purity of the monomers that are used. These polymerization properties include but are not limited to, rate of polymerization and stability of the monomer during storage. Another advantage of substantially pure alkyl cyanoacrylates is that compositions incorporating substantially pure alkyl cyanoacrylates require smaller amounts of additives, e.g., inhibitors, stabilizers and the like, to obtain a desired result that would otherwise have require greater amounts of the same additive.

[0021] Another embodiment of the present invention provides a method for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass by administering a composition of the present invention with an administering means, including a means for stabilizing fluid flow distal or proximal to the body space being treated, and a means for delivering the composition to the desired body space. An embodiment of the administering means is where the means for stabilizing

fluid flow distal or proximal to the body space being treated is in a first device, and the means for delivering the composition to the desired body space is in a second device. An embodiment of the first device includes a temporary inflatable balloon, or like structure, that is inflated to stabilize fluid flow distal or proximal to the body space to be treated, and deflated for removal after some period after the composition has been delivered. Optionally the balloon structure may be juxtaposed adjacent to the body space where the composition is deposited, and inflated such that the balloon structure maintains the composition at the body space while the composition is polymerizing, and deflated for removal after some period after the composition has been delivered. An embodiment of the the second device includes a catheter, or like device for delivering and depositing the composition of the present invention at a desired location. Another embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated, and the means for delivering the composition to the desired body space are within a single device or apparatus.

[0022] The types of unfilled volumes or spaces within the scope of the present invention includes, but are not limited to the following instances.

[0023] For example, one aspect of the present invention is a method of filling, occluding, partially filling or partially occluding an existing space, such as, a lumen of a passageway in the body, e.g., a blood vessel, a duct, an aneurysm, or a fistula. Examples of the types treatments covered by this method of use, include but are not limited to the following. The present invention is useful as a method of treating arteriovenous malformations (AVM) where the blood vessel(s) that feed the AVM are occluded thereby cutting off the blood supply to the AVM. The present invention is useful as a method to ablate diseased or undesired tissue by cutting off the tissue's blood supply. In particular, the present invention is useful as a method of treating a tumor having a discrete blood supply, where the blood vessel(s) that feed the tumor are occluded thereby cutting off the blood supply to the tumor resulting in diminished growth or death of the tumor. The present invention is useful as a method of

preventing or mitigating the development of an aneurysm by creating a partial occlusion at a location in the blood vessel selected to modify the fluid dynamics within the vessel to mitigate the formation or development of an aneurysm. The present invention is useful as a non-surgical method of treating symptomatic uterine leiomyomas by embolizing/occluding the uterine artery. This method has been reported using a non alkyl cyanoacrylate composition in *Journal of Vascular and Intervention Radiology*, 10:891-894, July-August 1999. The present invention is useful as a method of sterilizing a female mammal by occluding the fallopian tubes thereby preventing the passage of the eggs from the ovaries to the uterus. The use of an occluding agent to sterilize a female mammal is disclosed in U.S. Patent No. 5,989,580 "Method of Sterilizing Female Mammals", herein incorporated by reference. The methods disclosed in this patent can be advantageously applied using the compositions of the present invention, and are within the scope of the present invention. The present invention is useful for obliterating the left atrial appendage. The left atrial appendage is derived from the left wall of the primary atrium. It has been observed that patients with atrial fibrillation have a predilection for thrombus to form in the left atrial appendage. A review of this condition and the current status of treatment is disclosed in the article, "Left Atrial Appendage: structure, function, and role in thromboembolism" N.M. Al-Saady, et. al. The present invention provides an advantageous method of obliterating the left atrial appendage.

[0024] Another aspect of the present embodiment is a method of filling, occluding, partially filling or partially occluding a space created by a transiently placed external device, such as, a catheter balloon, a space created by a transiently placed external device, e.g., a catheter or like device. Examples of the types of treatments covered by this method of use include, but are not limited to the following. The present invention is useful as a method of treating an aneurysm by filling the space within the aneurysm with a composition of the present invention, where the composition polymerizes in the space within the aneurysm, thereby preventing the rupture of the aneurysm. The present method of treatment can be practiced using an administering means, including a means for stabilizing fluid flow distal or proximal to

the body space being treated, and a means for delivering the composition to the desired body space. An embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated is in a first device, and the means for delivering the composition to the desired body space is in a second device. An embodiment of the first device includes a temporary inflatable balloon, or like structure, that is inflated to stabilize fluid flow distal or proximal to the body space to be treated, and deflated for removal after some period after the composition has been delivered. Optionally the balloon structure may be juxtaposed adjacent to the body space where the composition is deposited, and inflated such that the balloon structure maintains the composition at the body space while the composition is polymerizing, and deflated for removal after some period after the composition has been delivered. An embodiment of the the second device includes a catheter, or like device for delivering and depositing the composition of the present invention at a desired location. Another embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated, and the means for delivering the composition to the desired body space are within a single device or apparatus. Such apparatuses include, but are not limited to, catheters, catheter coils, catheter wires, catheter balloons, or like devices. Many examples of such devices are known to those of ordinary skill in the art. For example, U.S. Patent No. 5,795,331 "Balloon Catheter For Occluding Aneurysms of Branched Vessels", incorporated herein by reference, discloses a device and methods for delivering compositions, such as those of the present invention. U.S. Patent No. 5,882,334 "Balloon/Delivery Catheter Assembly With Adjustable Balloon Positioning," incorporated herein by reference, assigned to Target Therapeutics, San Jose, California, and U.S. Patent No. 6,015,424 "Apparatus and Method For Vascular Embolization", incorporated herein by reference, assigned to MicroVention, Inc., Aliso Viejo, California, describe like devices that can be employed in practicing the present invention.

[0025] The present invention may also be practiced following the procedure and utilizing like devices described in **Neurosurgery**, Vol. 31, No. 3, September 1992,

page 591 "Carotid-Cavernous Fistula Caused by a Ruptured Intra-cavernous Aneurysm: Endovascular Treatment by Electrothrombosis with Detailable Coils."

[0026] Another aspect of the present invention provides a method of filling, occluding, partially filling or partially occluding a space created or resulting from a procedure, such as with the excision of tissue, or insufflation. Examples of the types of treatments covered by this method of use include, but are not limited to, the following. The present invention is useful as a method of treating or mitigating capillary oozing.

[0027] Another aspect of the present invention provides a method of filling, occluding, partially filling or partially occluding a space created by the placement or implantation of an object, such as, a medical device. Examples of the types of uses covered by this method of use include, but are not limited to the following. The present invention is useful as a method of restoring the normal fluid dynamics at the peripheral edges of a vascular stent by filling the dead spaces between the stent and the lumen wall created by the implantation of the stent.

[0028] Another aspect of the present invention is a method of filling, occluding, partially filling or partially occluding a space created by the composition itself, such as, where the composition is used as a bulking agent. Examples of the types of uses covered by this method of use include, but are not limited to the following. For example, a method of recreating the normal contours to skin following an adverse event, such as, physical trauma.

[0029] Another embodiment of the present invention provides a method of affixing therapeutics, chemotherapeutics, radiation delivery devices, gene therapy compositions to a desired location where the active agents can be advantageously maintained in proximity to the desired location. The active agent is then release gradually as the resultant aggregate structure from the composition of the present invention is biodegraded. Alternatively, the composition of the present invention can

be modified to allow for a specific rate of delivery. This use is particularly beneficial in the treatment of tumors that are ideally treated by localized dosages of chemotherapy or radiation. An advantage of this method is that the patient would not be subjected to as large of a dose of the therapeutic or radiation as would be necessary, if the therapeutic or radiation was administered on a systemic basis.

[0030] Another embodiment of the present invention provides a method of utilizing magnetically controlled particles embedded in a composition of the present invention to deploy the composition to a desired location. The use of magnetically controlled particles as medical probes is described in the following references, incorporated herein in their entirety: "Magnetic Probe for the Stereotaxic Thrombosis of Intracranial Aneurysms," Alksne, J.F., et. al, *Journal of Neurology,* Neurosurgery and Psychiatry, 1967 April, 30(2):159-62; "Magnetically Controlled Focal Intravascular Thrombosis in Dogs" Alksne, J.F., et. al, *Journal of Neurosurgery*, 1966 Nov, 25(5):516-25; "Thrombosis of Intracranial Aneurysms - An experimental approach utilizing magnetically controlled iron particles" Alksne, J.F., et. al, *Radiology* 1966 Feb. 86(2):342-3

[0031] Another embodiment of the present invention provides a method of adhering, joining, connecting or affixing a first section of tissue to a second section of tissue. Examples of the types of uses covered by this method of use include, but are not limited to the following. The present invention is useful as a method of adhering, joining, or connecting two blood vessels, e.g., anastomoses, where blood vessels are quickly and efficiently adhered, joined or connected, under surgical conditions without the use of sutures or staples. The present invention is useful as a method of treating primary wounds or wounds that require immediate intervention, such as, trauma wounds, where the compositions of the present invention are used to temporarily close the wound to minimize the lost of fluids due to evaporation, and to mitigate infection.

[0032] Another embodiment of the present invention provides a method of adhering, joining, connecting, or affixing tissue to a non-tissue surface, such as a medical device. Examples of the types of uses covered by this method of use include, but are not limited to the following. The present invention is useful as a method of implanting or securing venous valves, replacement heart valves, or stents at their desired location.

[0033] The aforementioned uses are possible because the compositions of the present invention remain in a controllable state for a period of time in excess of 1 second after being deployed from an administration device. This property allows the practitioner to incremental maneuver the deployment of the composition to its most ideal location, even though the composition had been partially deployed distal to the deployment device.

[0034] For instance, the compositions of the present invention have adequate cohesion to maintain its continuity once it is outside of the deployment device. Without adequate cohesion the composition would break into smaller aggregates dispersing into the blood flow. Additionally, the compositions of the present invention have appropriate adhesion properties so that a deployed composition adheres to the immediate location where it is deployed so that the resultant aggregate of the monomer is placed where it is desired.

[0035] The compositions of the present invention have polymerization rates, such that, the practitioner can effect the desired amount of penetration of the composition into a particular type of space. A composition that polymerizes too quickly would hinder penetration, conversely a composition that polymerizes too slowly would make it difficult to precisely place the polymerized composition including the resultant aggregate of the monomer.

[0036] Another embodiment of the present invention provides a method for selectively creating an embolic blockage in the lumen of a blood vessel, duct, fistula or other like body passageways.

[0037] Another embodiment of the present invention provides a method of treating arteriovenous malformation (AVM)

[0038] As used herein the terms "adhesion" or "adhesive" means the characteristic or tendency of a material to be attracted to the surface of a second material. Adhesion occurs as the result of interactions between two materials. Depending on the characteristics of the second material relative to the first material, adhesion may or may not occur. For a single material, e.g., the composition of the present invention, the presence of adhesion is demonstrated by a material sticking to the wall of a lumen of blood vessel, i.e., there is adhesion between the material and the lumen wall. Conversely, the absence of adhesion is demonstrated for the same material where a micro-catheter tip used to deposit the material can be removed from the material, i.e., there is little adhesion between the material and micro-catheter tip.

[0039] As used herein the term "anionic environment" refers to an ionic environment in which the net charge is negative. Essentially an anionic environment is any aqueous system with pH > 7. For example, a body fluid such as blood is an anionic environment.

[0040] As used herein the term "alkyl" refers to chains of carbon atoms which can be linear or branched, saturated or unsaturated.

[0041] As used herein the term "cohesion", "cohesive", or "cohesivity" means the characteristic or tendency of a liquid or semi-liquid material to maintain its integrity while being manipulated. For example, this characteristic is demonstrated by a material or composition remaining intact as a single mass when introduced into a

stationary fluid, or a fluid stream in motion, such as, blood. Lack of cohesive integrity results in the composition breaking up into multiple smaller subunits.

[0042] As used herein the term "embolic agent" refers to a non-naturally occurring composition introduced into a body cavity or the lumen of a blood vessel, duct, fistula or other like body passageways for the purpose of forming an embolic block.

[0043] As used herein the term "embolic block" or "embolic blockage" or occlusion refers to the end result from the administration of a composition useful as an embolic agent. The resulting embolic block mechanically blocks, totally or partially, the lumen of a blood vessel, duct, fistula or other like body passageways; or in a like manner forms an occlusion within a cavity, such as an aneurysm.

[0044] As used herein the term "alkyl esterified fatty acid" means a fatty acid derivatized to form an ester functional group with an alkyl moiety, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. Suitable fatty acids are carboxylic acids containing from 1 carbon (i.e., acetic acid) through 17 carbons atoms (i.e. stearic acid).

[0045] As used herein the term "opacificant agent" is compound or composition which selectively absorbs or deflects radiation making the material visible under x-ray, or any like imaging technique. Typically such agents include, iodinated oils, and brominated oils, as well as commercially available compositions, such as Pantopaque™, Lipiodol and Ethiodol. These commercially available compositions acts as opacificant agents, and also dilute the amount of liquid monomer thereby slowing the rate of polymerization. In addition certain metals, such as, gold, platinum, palladium tantalum, titanium, tungsten as well as alloys and mixtures therof. Salts such as barium sulfate and the like, have properties enabling them to act as opacificant agents.

[0046] As used herein the term "polymerization retardant" means an agent that can stop or slow down the rate of polymerization. Examples of such agents are pure phosphoric acid, and 85% phosphoric acid. Certain opacificant agents, such as Pantopaque™, Lipiodol™ and Ethiodol™ can also function as a polymerization retardant by diluting the amount of liquid monomer and hence slowing polymerization rate.

[0047] As used herein the terms "a space" and "a body space" refer to an unfilled volume or cavity in a mass. Examples of such spaces, include but are not limited by the following, an existing space within a mass, such as, the lumen of a blood vessel, the sac of an aneurysm; a space created by a transiently placed external device, such as, a catheter or like device; a space created by a procedure, such as, an excision or like procedure; a space created by implantation of an object, such as, a stent or like device; or a space created by the composition.

[0048] As used herein the term "stability" refers to the ability of a monomer component to resist degradation or polymerization after preparation but prior to use.

[0049] As used herein the term "inhibitor agent" refers to an agent which stabilizes a monomer composition by inhibiting polymerization. Within the context of the current invention, this term refers to agents that stabilize and inhibit polymerization by various mechanisms.

[0050] As used herein the term "deployment device" refers a device used to deploy compositions, such as, those of the present invention. Examples of such devices, include but are not limited the devices disclosed in U.S. Patent No. 5,882,334 "Balloon/delivery Catheter Assembly with Adjustable Balloon Positioning," incorporated herein by reference.

[0051] As used herein the term "oligomer" refers to chains of polymerizable monomers containing from 2 to about 20 repeating monomer units. Such chains may be linear or branched.

[0052] The present invention is a composition formed from alkyl cyanoacrylate monomeric units, such as, methyl, *n*-butyl, isobutyl, *n*-hexyl and 2-hexyl cyanoacrylate, a plasticizer, an opacificant agent and a thickening agent (i.e. an oligomer of a polymerizable monomer. The composition forms into its resultant aggregate structure, i.e., an oligomer or polymer, when it comes in contact with an anionic environment, such as, blood or tissue. The resultant aggregate composition has characteristics which makes it particularly well suited as an embolic agent.

[0053] "Plasticizers" are liquid materials which are added to solid polymers to render such polymers flexible. To function as plasticizers such liquid materials must be chosen to be compatible on a molecular scale with the specific polymer being plasticized. To be useful in the present invention the chosen plasticizer must be biocompatible. The term "biocompatible plasticizer" refers to any material which is soluble or dispersible in alkyl cyanoacrylate, which increases the flexibility of the resulting polymer, and which is compatible with the implant site in the body. Suitable plasticizers are well known in the art and include those disclosed in U.S. Pat. Nos. 2,784,127 and 4,444,933 the disclosures of both of which are incorporated herein by reference in their entirety. Specific stabilizers include by way of example, but are not limited to, alkyl esters of fatty acids such as alkyl myristates, alkyl laureates, alkyl stearates, and alkyl succinates. Other plasticizers useful in the present invention include by way of example, but are not limited to, acetyl tri-n-butyl citrate, butyl benzyl phthalate, dibutyl phthalate, diethyl phthalate, dimethyl phthalate, dioctylphthalate, n-butyryl tri-n-hexyl citrate, benzoate esters of di- and poly-hydroxy branched aliphatic compounds, tri(p-cresyl) phosphate, and the like. Preferred plasticizers for use in this invention are alkyl esters of fatty acids of 12 to 18 carbon atoms independently having from 1 to 6 carbon atoms in each alkyl group. A particularly preferred plasticizer is ethyl myristate.

[0054] The composition of the present invention is used by combining the monomer component and second component. Upon mixing of the components, the invention is administered into the lumen of a blood vessel, duct, fistula or other like body passageways. The characteristics of the present invention permit its accurate placement in the lumen. Contact with an anionic environment, such as blood or tissue causes the composition to polymerize. The size of the resultant embolic block formed is determined by the amount of composition administered.

[0055] Alternately, the first component and second component of the present invention can be combined and supplied as a single unit. Depending upon storage conditions and required storage stability the compositions of the present invention may be supplied as a system including separate first component and second component units or as a system including a single combined unit.

[0056] The characteristics of the composition of the invention can be modified for a specific purpose or environment for which the embolic agent is intended to be utilized. For example, changes in the length and isomeric configuration of the alkyl side chains can alter the brittleness of the resultant aggregate of cyanoacrylate monomers. Alkyl chains that result in the formation of smaller aggregates tend to be less brittle, while larger aggregates tend to be less flexible. In addition, by combining monomers with different alkyl side chains the characteristics of the resultant polymer can be modified to what is optimal for a desired application.

[0057] The monomer components of the present invention are prepared from commercially available starting materials following procedures known to those of ordinary skill in the art such as the procedures described in U.S. Patents 3,728,375; 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826 which are hereby incorporated by reference.

[0058] In the context of the present invention "stabilizer" and "inhibitor" have essentially the same meaning. Different inhibitors have different physical characteristics and thereby functions to alter the final properties of the composition. For example, hydroquinone is primarily an inhibitor for high energy free radicals; *p*-methoxyphenol is primarily an inhibitor for low energy free radicals. Other free radical inhibitors useful in the present invention include but are not limited to butylated hydroxy toluene, butylated hydroxy anisol, ascorbic acid (vitamin C), vitamin E, beta-carotene, isoeugenol. Acids acidic inhibitors inhibit anionic polymerization and acts to control the rate of such polymerization. Such acidic inhibitors useful in the present invention include but are not limited to phosphoric acid, acetic acid, lactic acid, ascorbic acid, and citric acid. The preferred acidic inhibitor in the present invention is phosphoric acid.

[0059] The quantity of inhibitors used is measured in terms of parts per million of alkyl cyanoacrylate. All of the inhibitors of the present invention may be used in quantities ranging from about 1 ppm to about 500 ppm. For typical compositions, hydroquinone is in the range of about 50 to 150 parts per million (PPM), *p*-methoxyphenol in the range of about 50 to 150 PPM, and phosphoric acid in the range of about 125 to 375 PPM, more preferred is hydroquinone in the range of about 75 to 125 PPM, *p*-methoxyphenol in the range of about 75 to 125 PPM, and phosphoric acid in the range of about 187.5 to 312.5 PPM, and most preferred is hydroquinone in the range of about 95 to 105 PPM, *p*-methoxyphenol in the range of about 95 to 105 PPM, and phosphoric acid in the range of about 50-500 PPM. Similarly, for a monomer component including of 90% *n*-hexyl cyanoacrylate and 10% methyl cyanoacrylate, hydroquinone is in the range of about 50 to 150 parts per million (PPM), *p*-methoxyphenol is in the range of about 50 to 150 PPM, and acetic acid is in the range of about 50 to 500 PPM, more preferred is hydroquinone in the range of about 75 to 125 PPM, *p*-methoxyphenol in the range of about 75 to 125 PPM and acetic acid in the range of about 50 to 500 PPM, and most preferred is hydroquinone in the range of about 95 to 105 PPM, *p*-methoxyphenol in the range of about 95 to 105 PPM, and acetic acid in the range of about 150 to 500 PPM.

[0060] The oligomers of the second component of the present invention may be prepared from any polymerizable organic monomer using any standard oligomerization technique. To be useful in the present invention the oligomers must be soluble in the monomer of the first component and the plasticizer of the second component. In the present invention the oligomers function as viscosity modifiers and as such contribute to the cohesively of the compositions. The oligomers may be prepared from on or more of the same polymerizable organic monomers of the first component of a particular composition if this invention. Alternatively the oligomers may be prepared from monomers different from those used in the first component of a particular composition if this invention. The preferred oligomers of the second component of a particular composition of present invention are those prepared from one the same polymerizable organic monomers of the first component of the same particular composition. More preferred are oligomers of alkyl cyanoacrylates and most preferred are oligomers of n-hexyl cyanoacrylate and 2-hexyl cyanoacrylates.

[0061] The second component functions as an opacificant agent and a polymerization retardant. To this end, the second component includes an iodinated oil, such as Ethiodol™, or a brominated oil. Typically the iodinated oil is mixed as some percent of the total volume of the final composition. The percentage solution of iodinated oil used will influence the polymerization rate and opacity of the composition. Generally advantageous ranges are from about 17% to 66%, preferably about 33%.

[0062] Alternatively, the second component can be a composition including, a opacificant material, such as gold, platinum, palladium, tantalum, titanium, tungsten and barium sulfate and the like; an alkyl cyanoacrylate polymer material, and an esterified fatty acid, where the fatty acids have 3 carbon atoms, for example, alkyl butyrate to 17 carbons, for example, alkyl stearate, preferred are, alkyl laurate, alkyl myristate, alkyl palmatate, and alkyl stearate, most preferred is alkyl myristate, and most especially preferred is ethyl myristate. The opacificant material is used in a fine

powder form, typically, with individual particles sized no larger than about 7 microns in diameter, preferably about 5 microns, most preferred about 2 microns and most especially preferred is 1 micron or smaller.

[0063] The amount of opacificant material used relative to alkyl cyanoacrylate polymer will vary according to the specific materials. Factors that influence the determination of the ratio include the amount and size of the particles that are being coated by the alkyl cyanoacrylate polymer. For example, for 2-hexyl cyanoacrylate and gold, 2 g of 2-hexyl cyanoacrylate is used per 100 g of powdered gold (particle size of about 5 ± 2 microns) being coated. For example, for *n*-hexyl cyanoacrylate and gold, 2 mg of *n*-hexyl cyanoacrylate is used per 1 gm of gold at a particle size of about 2 to 10 μm, preferably about 0.1 to 1.0 μm , most preferably about 1 μm . The amounts vary accordingly with the opacificant material being coated by the alkyl cyanoacrylate. The alkyl cyanoacrylate and opacificant material are mechanically mixed by processing the alkyl cyanoacrylate into small particulate masses, and mixing with the finely powdered opacificant material. The alkyl cyanoacrylate polymer coated material is then stored in a plasticizer, which serves as a medium where the alkyl cyanoacrylate polymer coated material is maintained prior to use, and as a medium, which when contacted with the monomer component will not interfere with the polymerization of the composition.

[0064] The characteristics of the composition of the invention can be modified for a specific application or environment in which the composition is intended to be utilized. For example, changes in the length and isomeric configuration of the alkyl side chains can alter the brittleness of a polymer formed from a cyanoacrylate monomer. Alkyl chains that result in the formation of smaller aggregates tend to be less brittle, while larger aggregates tend to be less flexible. Another method of modifying the characteristics of a polymer is to use a composition including of two or more types of alkyl cyanoacrylate monomers in combination with the appropriate inhibitors.

[0065] For example, a composition comprised of a monomer component including of 2-hexyl cyanoacrylate and phosphoric acid; and a second component including of 2-hexyl cyanoacrylate polymer, gold, and ethyl myristate results in composition A. Alternatively, a composition comprised of a monomer component including of 90% *n*-hexyl cyanoacrylate and 10% methyl cyanoacrylate, hydroquinone, *p*-methoxyphenol and acetic acid; and a second component including of *n*-hexyl cyanoacrylate polymer, gold, and ethyl myristate results in composition B

[0066] Both compositions A and B have excellent cohesion properties. When introduced into a stationary fluid, or a fluid stream in motion, such as, the lumen of a blood vessel or other like passageway, the composition tend to stick together to itself remaining intact as a single mass or aggregate. This permits the polymers to be discretely deposited or placed at the desired location without the hazard of having potions of the composition breaking away and depositing at undesired locales. Compositions A and B to have viscosity that permit the injection of the liquid composition into a lumen of a blood vessel, duct, fistula or passageway in the body without using excessive pressure.

[0067] However, compositions A and B have different adhesion, polymerization and tactile properties. Compositions A is less adhesive than compositions B, and its polymerization profile upon contact with an anionic environment, such as, tissue or blood, is a transition from a liquid state to a semi-solid state before completing in a soft solid state, and the resultant polymer is a soft, flexible solid. With these properties Composition A is ideally suited for applications where the composition must penetrate further into anionic environment before arriving at the point of final placement. A preferred use is the treatment of arteriovenous malformations, also known as AVM. Composition A is also ideally suited for the treatment of longer type urinary fistulas, this is because preferred treatment requires greater penetration into cavity space by the liquid composition. Additional applications suited for Composition A are creating a tubal occlusion, and surgical adhesions. For example, a

composition of the present invention is applied to raw intraperitoneal tissue to prevent the tissue from adhering to itself or other tissue.

[0068] Composition B is more adhesive than composition A, its polymerization profile upon contact with an anionic environment, such as, tissue or blood, is a transition from a liquid state to a soft solid and completing as a firm solid. With these properties composition B is ideally suited for applications where the composition must quickly adhere and polymerize in the surrounding anionic environment. Particularly advantageous applications for composition B is treatment of various types of aneurysms.

[0069] Another advantageous application for composition B is the treatment of fistulas, particularly those where it is desirable to have the resultant aggregate structure form close to the point of deployment.

[0070] Still another advantageous use for composition B is for the maintenance of homeostasis during surgery, such as, during hepatectomy, renal surgery, and during gynecologic tumor surgery.

[0071] Further, composition B can be used to treat certain types of varicose veins, where composition B is injected into the portal vein.

[0072] The present invention is useful for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space"). In particular, the composition is useful for filling an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition; the composition is also useful for adhering tissue to tissue, or adhering tissue to a device. The composition has the property of polymerizing when it comes in contact with an anionic environment, or when it is

deployed *in situ* in an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition.

[0073] The present invention is useful as an embolic agent that selectively creates an embolic blockage in the lumen of a blood vessel, duct, fistula or other like body passageways.

[0074] The present invention can be prepared and maintained as a first component and second component until needed or the components may be combined and stored. Storage conditions depend upon the stabilizers chosen.

[0075] The cohesive characteristics of the invention are such that when the composition in administered into an anionic fluid environment, such as blood, the composition forms a single aggregate structure. Additionally, the adhesive characteristics are such that the composition attaches to the lumen of vessel, duct, fistula or other like body passageways, but not to the degree where the device depositing the composition will become fixed to it before the practitioner can remove it.

[0076] The present invention is radiopaque. Although this characteristic is not necessary for its function as an embolic agent, radiopacity allows the embolic block to be observed with x-ray or other such imaging techniques.

[0077] The rate of heat released during polymerization of the present invention is low enough such that the heat does not adversely effect surrounding tissues that may be heat sensitive, such as brain tissue.

[0078] The present invention and its biodegradation products are sufficiently non-histotoxic and non-cytotoxic so that its presence is well tolerated in the body.

[0079] The composition of the present invention is useful for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space").

[0080] The present invention provides a method for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass. The types of unfilled volumes or spaces within the scope of the present invention includes, but are not limited to the following instances.

[0081] For example, the present invention is used as a method of filling, occluding, partially filling or partially occluding an existing space, such as, a lumen of a passageway in the body, e.g., a blood vessel, a duct, an aneurysm, or a fistula. Examples of the types treatments covered by this method of use, include but are not limited to the following. The present invention is useful as a method of treating arteriovenous malformations (AVM) where the blood vessel(s) that feed the AVM are occluded thereby cutting off the blood supply to the AVM. The present invention is useful as a method to ablate diseased or undesired tissue by cutting off the tissue's blood supply. In particular, the present invention is useful as a method of treating a tumor having a discrete blood supply, where the blood vessel(s) that feed the tumor are occluded thereby cutting off the blood supply to the tumor resulting in diminished growth or death of the tumor. The present invention is useful as a method of preventing or mitigating the development of an aneurysm by creating a partial occlusion at a location in the blood vessel selected to modify the fluid dynamics within the vessel to mitigate the formation or development of an aneurysm. The present invention is useful as a non-surgical method of treating symptomatic uterine leiomyomas by embolizing/occluding the uterine artery. This method has been reported using a non alkyl cyanoacrylate composition in the *Journal of Vascular and Interventional Radiology,* 10:891-894, July-August 1999. The present invention is

useful as a method of sterilizing a female mammal by occluding the fallopian tubes thereby preventing the passage of the eggs from the ovaries to the uterus. The use of an occluding agent to sterilize a female mammal is disclosed in U.S. Patent No. 5,989,580 "Method of Sterilizing Female Mammals," herein incorporated by reference. The methods disclosed in this patent can be advantageously applied using the compositions of the present invention, and are within the scope of the present invention.

[0082] The present invention is an embolic agent that provides a method for selectively creating and placing an embolic blockage which mechanically blocks, totally or partially, the lumen of a blood vessel, duct, fistula or other body passageway. In particular, the current invention is particularly useful in blocking, totally or partially, or diverting the flow of blood through the lumen.

[0083] The present invention can be advantageously used to block blood flow to certain tissues or areas. For example, the present invention can be used to treat arteriovenous malformation (AVM). An AVM is a collection of abnormal blood vessels which are neither arteries or veins. These vessels are packed closely together to form the nidus of the AVM. Blood flow into the AVM nidus is through thinned, enlarged, tortuous vessels and is rapidly shunted into draining veins because the nidus contains no arterioles or capillaries to provide high resistance. Clinical symptoms experienced because of AVMs are bleeding, re-direction of blood from nearby normal structures, or seizures. The primary clinical problem associated with cerebral AVM is the potential for lethal hemorrhage. The current standard of care for treating AVMs is surgical removal, high energy radiation or embolization with particular devices.

[0084] Further, the present invention can be used for treating cancer by diverting or blocking blood flow to tumors, the present invention is particularly useful for treating tumors in areas that are not easily accessible for surgical intervention, for example, brain tumors.

[0085] Other advantageous uses of the present invention are for aortopulmonary closure; treatment of artery pseudoaneursym; hepatic artery vascular occlusion and for temporary vascular occlusion during co-administration of cytotoxic drugs; treatment of other types of vessels, for example, the composition can be used for creating tubal occlusions, fallopian tube occlusions, vas deferens occlusions, and urinary occlusions.

[0086] The present invention provides a method of filling, occluding, partially filling or partially occluding a space created by a transiently placed external device, such as, a catheter balloon. Examples of the types of treatments covered by this method of use include, but are not limited to the following. The present invention is useful as a method of treating an aneurysm by filling the space within the aneurysm with a composition of the present invention, where the composition polymerizes in the space within the aneurysm, thereby preventing the rupture of the aneurysm. This treatment can be practiced using an administering means, including a means for stabilizing fluid flow distal or proximal to the body space being treated, and a means for delivering the composition to the desired body space. An embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated is in a first device, and the means for delivering the composition to the desired body space is in a second device. An embodiment of the first device includes a temporary inflatable balloon, or like structure, that is inflated to stabilize fluid flow distal or proximal to the body space to be treated, and deflated for removal after some period after the composition has been delivered. Optionally the balloon structure may be juxtaposed adjacent to the body space where the composition is deposited, and inflated such that the balloon structure maintains the composition at the body space while the composition is polymerizing, and deflated for removal after some period after the composition has been delivered. An embodiment of the the second device includes a catheter, or like device for delivering and depositing the composition of the present invention at a desired location. Another embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated, and the means for delivering the composition to the desired body space are within a single device or apparatus. Such

apparatuses include, but are not limited to, catheters, catheter coils, catheter wires, catheter balloons, or like devices. Many examples of such devices are known to those of ordinary skill in the art. For example, U.S. Patent No. 5,795,331 "Balloon Catheter For Occluding Aneurysms of Branched Vessels", incorporated herein by reference, discloses a device and methods for delivering compositions, such as those of the present invention. The device described combines an inflatable balloon with a catheter as a single apparatus, where the balloon is distal or proximal to the opening of the catheter. The present invention has been practiced following the procedure and utilizing like devices described in **Neurosurgery**, Vol. 31, No. 3, September 1992, page 591 "Carotid-Cavernous Fistula Caused by a Ruptured Intra-cavernous Aneurysm: Endovascular Treatment by Electrothrombosis with Detailable Coils." The reference describes a procedure using a temporary inflatable balloon catheter, and a catheter for placement of a detachable platinum coil. A temporary balloon occlusion is performed proximally to a fistula, and then followed by the insertion of a platinum detachable coil into the fistula. The temporary balloon occlusion stabilizes the immediate environment near the fistula from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow, while a thrombus forms around the platinum wire. In the present invention, a temporary balloon occlusion performs a similar function of stabilizing the immediate environment near the body space to be treated, for example, a fistula or aneurysm, from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow. The temporary balloon, optionally, may also be used to temporarily form a seal at the opening of the body space, while the composition that had been deposited in the body space is polymerizing to its final form. After a period of time sufficient for the polymerization to be completed, the temporary balloon catheter is deflated and withdrawn.

[0087] The present invention also provides a method of filling, occluding, partially filling or partially occluding a space created or resulting from a procedure, such as with the excision of tissue, or insufflation. Examples of the types of treatments covered by this method of use include, but are not limited to the following.

The present invention is useful as a method of treating oozing capillaries following an excision procedure.

[0088] The present invention further provides a method of filling, occluding, partially filling or partially occluding a space created by the placement or implantation of an object, such as, a medical device. Examples of the types of uses covered by this method of use include, but are not limited to the following. The present invention is useful as a method of restoring the normal fluid dynamics at the peripheral edges of a vascular stent by filling the dead spaces between the stent and the lumen wall created by the implantation of the stent.

[0089] Still another advantageous use is the controlling and smoothing the blood flow around stents. A major complication from the balloon angioplasty and the use of stents is disruption of the smooth flow of blood past and around the stent which can lead to the formation of blood clots and their associated complications. The composition of the present invention can be used to modify and make regular the slip streams of blood through and adjacent to the stent to mitigate or alleviate the cause of the turbulence, and such turbulence causing states.

[0090] The present invention further provides a method of filling, occluding, partially filling or partially occluding a space created by the composition itself, such as, where the composition is used as a bulking agent. Examples of the types of uses covered by this method of use include, but are not limited to the following. For example, a method of recreating normal external contours, such as following physical trauma.

[0091] The monomer component and second component of the present invention are combined just prior to use. The composition of the present invention is administered using any type of deployment device. The term "deployment device" refers to a device used to deploy fluids or compositions similar to those of the present invention, such as, a needle, catheter devices, catheter balloon, stereotaxic placement

devices, or the like. Methods for using these devices are readily known to one of ordinary skill in the art, and such devices are commercially available. Such devices and methods are readily known to those of ordinary skill in art. For example in U.S. Patent 5,925,683 "Liquid Embolic Agents", herein incorporated by reference, there is disclosed a method for introducing liquid embolic agents/solutions into the human body to form precipitated embolic occlusion masses, and also how this method is used for treating hepatic tumors using portal vein embolism. In U.S. Patent 5,702,361 "Method for Embolizing Blood Vessels", herein incorporated by reference, there is disclosed a method of embolizing a vascular site in a patient's blood vessel including of introducing, via a catheter, at the vascular site to be emobolized a non-particulate agent or a plurality of such agents, and delivering, via a catheter, to the vascular site a polymer composition including a biocompatible polymer, a biocompatible solvent and contrast agent, wherein the delivery is conducted under conditions where the polymer precipitate forms in situ at the vascular site resulting in the embolizing of the blood vessel and where the non-particulate agent is encapsulated within the precipitate. An administrating means can be used to deliver the composition of the present invention to a desired location, the administering means including, a means for stabilizing fluid flow distal or proximal to the body space being treated, and a means for delivering the composition to the desired body space. An embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated is in a first device, and the means for delivering the composition to the desired body space is in a second device. An embodiment of the first device includes a temporary inflatable balloon, or like structure, that is inflated to stabilize fluid flow distal or proximal to the body space to be treated, and deflated for removal after some period after the composition has been delivered. Optionally the balloon structure may be juxtaposed adjacent to the body space where the composition is deposited, and inflated such that the balloon structure maintains the composition at the body space while the composition is polymerizing, and deflated for removal after some period after the composition has been delivered. An embodiment of the the second device includes a catheter, or like device for delivering and depositing the composition of the present invention at a desired location. Another embodiment of the administering

means is where the means for stabilizing fluid flow distal or proximal to the body space being treated, and the means for delivering the composition to the desired body space are within a single device or apparatus. Such apparatuses include, but are not limited to, catheters, catheter coils, catheter wires, catheter balloons, or like devices. Many examples of such devices are known to those of ordinary skill in the art. For example, U.S. Patent No. 5,795,331 "Balloon Catheter For Occluding Aneurysms of Branched Vessels", incorporated herein by reference, discloses a device and methods for delivering compositions, such as those of the present invention. The device described combines an inflatable balloon with a catheter as a single apparatus, where the balloon is distal to the opening of the catheter. The present invention has been practiced following the procedure and utilizing like devices described in **Neurosurgery**, Vol. 31, No. 3, September 1992, page 591 "Carotid-Cavernous Fistula Caused by a Ruptured Intra-cavernous Aneurysm: Endovascular Treatment by Electrothrombosis with Detailable Coils." The reference describes a procedure using a temporary inflatable balloon catheter, and a catheter for placement of a detachable platinum coil. A temporary balloon occlusion is performed proximally to a fistula, and then followed by the insertion of a platinum detachable coil into the fistula. The temporary balloon occlusion stabilizes the immediate environment near the fistula from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow, while a thrombus forms around the platinum wire. In the present invention, a temporary balloon occlusion performs a similar function of stabilizing the immediate environment near the body space to be treated, for example, a fistula or aneurysm, from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow. The temporary balloon, optionally, may also be used to temporarily form a seal at the opening of the body space, while the composition that had been deposited in the body space is polymerizing to its final form. After a period of time sufficient for the polymerization to be completed, the temporary balloon catheter is deflated and withdrawn.

[0092] The composition of the present invention are administered with any type of commercially available needle, catheter devices, or stereotaxic placement devices,

preferably in conjunction with imaging technology that provides the practitioner with guidance as to the placement of the composition. The compositions of the present invention can be used advantageously in conjunction with any embolization method that employs an embolizing agent, occluding agent, or such composition that creates an embolic block, or occlusion, or otherwise in effect is used for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space"). Delivery can also be made with a micro catheter made from or coated with an agent that lessens the likelihood of accidental gluing of the device to the vessel, for example, hydrophilic coating and silicone derivative coatings.

[0093] The following examples are given to enable those of ordinary skill in the art to more clearly understand and to practice the present invention. The examples should not be considered as limiting the scope of the invention, but merely as illustrative and representative thereof.

EXAMPLE 1

Formulation of a typical first component

Material	Weight (G)	Moles
2-hexyl cyanoacrylate	1250	6.8964
hydroquinone	0.0764	0.000694
p-methoxyphenol	0.0874	0.000704
phosphoric acid	0.1693	0.001726

EXAMPLE 2

Preparation of a typical second component

To a Waring blender was added 0.50 G of sodium bicarbonate and 250 mL water. 18 mL was added dropwise into the center of blender while the blender was stirring on

the high setting. After the addition of was completed, the mixture was stirred for another minute. The resulting solid oligomer was isolated via filtration, washed with 2 portions of water followed by one portion of methanol and dried *in vacuo*. 2.0 G of the this oligo (2-hexyl cyanoacrylate) was combined with 100 g of powdered gold and placed was placed into a standard laboratory blender and blended for one minute. The blender was agitated constantly during the blending to ensure that the gold did not settle during the blending. 1.020 g portions of the blended material were placed into previously cleaned vessels and to each vessel was added 500 mg of ethyl myristate of 99.8% purity.

EXAMPLE 3

Comparison of catheter adhesion force for 2-hexyl cyanoacrylate and *n*-butyl cyanoacrylate compositions

This example demonstrates differences in adhesion to a catheter of an alkyl cyanoacrylate of the present invention and an n-butyl cyanoacrylate.

All the mixtures were injected through a TurboTracker™ micro- catheter device (Medi-tech/Boston Scientific, Watertown, MA). All mixtures were prepared immediately prior to use to prevent separation of the components or contamination. The catheter tips were placed at the bottom of 10 mm by 5 mm diameter wells filled with 0.2 mL of heparinized human whole blood. Through the micro-catheter, 0.15 mL of each embolic mixture was injected into each well, surrounding the tip of the micro catheter. Mixtures containing n-butyl cyanoacrylate were allowed to polymerize for 1.0 minute, and those containing 2-hexyl cyanoacrylate for 3.0 minutes. The micro-catheters were then extracted from the polymerized cyanoacrylates at a constant rate of 8.3 mm/sec (Model 1000 Materials Testing System; Instron, Canton, MA) and the forces required for extraction were measured and recorded. (Minibeam Force Transducer™, 25-lb capacity; Interface Advanced Force Measurement, Scottsdale, AZ). Five samples of each mixture were tested.

Comparison of the results was performed using the student *t* test.

Table 1

Composition	Alkyl cyanoacrylate	opacificant	plasticizer	Adhesion Force (N)
1	2-hexyl	33% gold powder	20% ethyl myristate	0.41 ± 0.14
2	2-hexyl			1.00 ± 0.23
3	2-hexyl	33% Ethiodol™		0.28 ± 0.12
4	2-hexyl	50% Ethiodol™		< 0.05
6	n-butyl	33% Ethiodol™		1.83 ± 0.21
7	n-butyl	50% Ethiodol™		0.34 ± 0.14

Ethiodol™ = iodinated castor oil

The data presented in table 1 clearly demonstrate that 2-hexyl cyanoacrylate compositions have significantly lower adhesion to the catheter than do the corresponding n-butyl cyanoacrylate compositions.

EXAMPLE 4

Formulation of a monomer component with *n*-hexyl cyanoacrylate and methyl cyanoacrylate

A. A monomer component with *n*-hexyl cyanoacrylate is formulated with the following materials, *n*-hexyl cyanoacrylate, hydroquinone, *p*-methoxyphenol and glacial acetic acid. The hydroquinone and *p*-methoxyphenol are kept under reduced pressure in a desiccator over a drying agent. The glacial acetic acid is taken up in a syringe and the syringe and the inhibitor is weighed, an amount of glacial acetic acid is added, and the syringe with the glacial acetic acid is re-weigh to determine the amount of glacial acetic acid that had been added. This process is repeated until the desired amount of glacial acetic acid is added.

The monomer component is analyzed by gas chromatography for purity under the following conditions.

Instrument Description: HP5890 Gas Chromatograph with HP chemstation software.

Column Description: Supelco Nukol (60 meters- length, I.D., 0.32 mm, Film Thickness 1μm)

Instrument Parameters:	Method 1
Injector Temperature:	220°C
Detector Temperature:	280°C
Head Pressure:	15 PSI
Air Pressure:	35 PSI
Hydrogen Pressure:	40 PSI
Aux.:	60 PSI
Initial Oven Temperature:	140°C for 20 min.
Ramp:	5°C/min.
Final Oven Temperature:	200°C for 50 min.
A Splitless System:	
Injection Volume:	1.0 microliter

The component is sufficient pure if the combined impurities present totals to less than 1%.

B. Following the procedures taught in Part A of the present Example, a monomer component with a combination of methyl cyanoacrylate and *n*-hexyl cyanoacrylate can be made.

In place of the amount of *n*-hexyl cyanoacrylate called for in the above procedure, a combination of methyl cyanoacrylate and *n*-hexyl cyanoacrylate is use. The amounts of each material used is determined according to the following ratio:

moles of methyl cyanoacrylate = 0.111 x moles *n*-hexyl cyanoacrylate

EXAMPLE 5

Comparison of cyanoacrylate compositions

For conformal endovascular obliteration utility

Methods and Materials

Transparent silicone models of aneurysms representing both narrow and wide neck configurations were constructed. Model A consisted of a straight 4mm tube with three 7mm aneurysms attached. The neck diameter was 3mm. Model B consisted of a helical 4mm tubing containing four aneurysms positioned along the greater curvature. Two were 5mm in diameter (1 having a 2mm neck, and the other having a 4mm neck), and two were 9mm in diameter (1 having a 3mm neck, and the other a three by 5mm neck). The helical model ended in a bifurcation; a 4mm wide neck aneurysm was positioned at the bifurcation to simulate a basiler tip aneurysm.

Twelve compounded cyanoacrylates were tested, six based upon the 2-hexyl cyanoacrylate / methyl cyanoacrylate monomers, six based upon the 1-hexyl cyanoacrylate / methyl cyanoacrylate monomers. Additives consisted of various oils, gold for opacification, and polymerization retardants. The silicone aneurysms were filled with heparinized pig blood, and were injected with microcatheters under direct visualization during static conditions, and under fluoroscopic guidance during pulsatile flow conditions.

Model A was filled with heparinized pig blood, and each of the twelve compounds was injected into three aneurysms, directly visualizing the degree of filing. The models were then radiographed, opened, and the contents examined by microscopy.

Model B was perfused with heparinized pig blood, pulsatile flow, 40 centimeters per second. The mixtures were introduced via micro-catheters; injection

was controlled with fluoroscopic visualization.

All twelve compounds remained cohesive and conformed nicely to the outline of the aneurysm. Many of the mixtures based upon the 2-hexyl monomer exhibited delayed polymerization, and could not be kept within the aneurysm lumen, even with adjacent balloon control of the infusion process. Four of the mixtures based upon the 1-hexyl monomer gave good cohesion, good conformation, remained within the aneurysm, and allowed some degree of angioplasty and remodeling of the arterial lumen by silicone balloon

[0094] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent to those of ordinary skill in the art in light of the teaching of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the claims.